

IN THE UNITED STATES PATENT OFFICE

Inventor : W. Roy KNOWLES, M.D.  
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Examiner: Vickie KIM



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2-21-01

RULE 1.132 DECLARATION

- 1) I am the inventor of record for the captioned patent application. I make this Declaration under 37 Code of Federal Regulations Rule 1.132.
- 2) I am a person of skill in the art of dermatology and the treatment of skin conditions including hair loss. Specifically, I was trained as and worked as a dermatological surgeon. I attended Southwestern Medical School (Dallas, Texas). I completed my internship at Letterman General hospital (San Francisco, California). I completed my residency at Baylor College of Medicine. I am Certified by the American Board of Dermatology. I have been appointed as a Fellow of the American Academy of Dermatology; a Fellow of the American Academy of Dermatological Surgery; Associate Editor of The Journal of Dermatologic Surgery and Oncology; a Clinical Associate Professor of Dermatology at the University of Texas Medical School; Clinical Associate Professor of Dermatology at Baylor College of Medicine; and Guest Lecturer

at University of Houston College of Pharmacy. I attach as an exhibit a copy of my *curriculum vitae*.

- 3) The prior art teaches away from my invention. The prior art - including the art of record - teaches the use of skin penetration enhancers. The prior art also teaches how to use minoxidil or progesterone in a topical formulation. The prior art, however, teaches away from combining either or both of these with a penetration enhancer. This is due to the widely-held assumption in the art that combining minoxidil (or progesterone) with a penetration enhancer would make the minoxidil (or progesterone) penetrate into the **systemic blood circulation** and thus precipitate known systemic side effects.
- 4) Minoxidil, for example, is known as "a potent anti-hypertensive." ✓ Bradbury at col.1, line 28-29. It affects heart rate and rhythm. It has thus been used as a cardiac drug. Over-dosage may, however, create cardiac arrhythmias. See Hoke at col.5, line 4-6 (systemic administration of finasteride® creates unwanted systemic side effects). The art thus teaches that minoxidil, if combined with a penetration enhancer, could precipitate cardiac arrhythmias.
- 5) Similarly, "testosterone blockers" (competitive anti-androgens which inhibit the binding of testosterone or DHT onto a cell

surface binding site, or inhibits the reduction of testosterone into DHT) have a key shortfall: their long term efficacy is compromised by their blocking of inhibition of gonadotropin secretion, which in turn increases testicular secretion of testosterone, which eventually overcomes the action of the testosterone blocker. Progesterone's "well documented" side effects include feminization and impotency, Hoke col.4, line 22-24, and other serious side effects such as decreased libido, and it "systemically disrupts the menstrual cycle in women," Orentreich.

- 6) Cardiac arrhythmias, feminization and impotency are side effects generally not acceptable for treating a non-life threatening condition like hair loss. Even the cited art of record acknowledges this. For example, Orentreich teaches that these side effects **preclude systemic use** of these compounds for skin disorders. Orentreich at col.1, line 45-52. Such "well documented" systemic side effects thus discourage using a penetration enhancer.
- 7) Dissuaded by the potential for these systemic side effects, no one has actually tested minoxidil or progesterone with a penetration enhancer. More to the point, contrary to the Examiner's assertion, combining minoxidil or progesterone with

a penetration enhancer has never been "utilized by the skilled artisan" at all, much less in "common practice." The references cited do not show that the combination was in fact utilized even once.

- 8) Bradbury. Bradbury does not enable one of skill in the art to practice my invention, because Bradbury would require undue experimentation. Bradbury discloses the cosmetic or therapeutic use of lupane triterpine compounds. In discussing lupane triterpines, Bradbury mentions **several thousand** other, miscellaneous compounds as "optional" additives. These include flavors (col.12, line 45-46), sweeteners (col.22, line 29-32) and motion sickness medicine (col. 24, line 64). These several thousand compounds can be potentially combined to make millions and millions of possible combinations. Bradbury does not say **which two or three** combinations among the millions to use. Bradbury does not teach **how much** of each compound to use. Discerning this would require testing each of the millions of possible chemical combinations. Each of these millions of tests would require using hair growth tests that - like the tests I performed - require several years to complete.

9) **Furthermore, Bradbury actively teaches away from my invention.**

In discussing the advantages of his own invention, Bradbury actively denigrates my approach. He says minoxidil *doesn't work well* and poses a significant cardiovascular *side effect risk*. He says, "One approach for growing hair involves the much publicized use of minoxidil [], a potent antihypertensive agent, as a hair growth promoting agent .... Unfortunately, not all people respond to minoxidil and the efficacy level is limited in those individuals who do exhibit a response." Bradbury, col. 1., line 31-33. Bradbury accurately reflects the prevailing assumption in the art - that minoxidil does not work well, and that its known, "potent" antihypertensive effects make it unattractive for systemic use with a penetration enhancer. This is why Bradbury dismisses minoxidil, penetration enhancer and testosterone blocker as just some of thousands of other "optional" ingredients like flavor, perfume and motion sickness medicine.

- 10) Bazzano. Bazzano does not disclose an "essential" (see below) claim element. I claim minoxidil + penetration enhancer. In contrast, Bazzano discloses minoxidil + retinoid. Bazzano at col.3, line 59-64. She says the

retinoid (in contrast to penetration enhancer) is therapeutically active: it "initiate[s] cell growth and differentiation (not initiated by minoxidil)." Id. at col.5, lines 17-42. In contrast to cell-growth initiating retinoids, Bazzano does not even mention penetration enhancers.

11) Bazzano teaches away from my invention - she says that it will not work. Bazzano says, "Minoxidil is recognized as being somewhat effective in producing new vellus hair growth and sparse terminal hair growth in a pre-selected group of subjects, However, its effect is far from satisfactory in most subjects. \* \* \* [M]inoxidil may not be able to sustain the growth of terminal hairs from vellus hairs on the scalp. In the majority of subjects with alopecia, terminal hair growth on the scalp may not be initiated or sustained by the topical application of minoxidil nor by its systemic administration." Bazzano at col.3, line 53-56; col.4, lines 49-54.

12) Bazzano also says that without retinoid, minoxidil lacks any "profound effect" and "cannot" produce a strong response. She says that, for retinoids and minoxidil, **"neither compound alone may have profound effects on advanced alopecias \* \* \*** the combination of these substances in the present invention

produces an effect **which cannot be produced by either compound separately.**" Bazzano at col.5, lines 17-42. Bazzano explains, "Retinoids can initiate cell growth and differentiation (not initiated by minoxidil)" required for hair growth. Id. In contrast, Bazzano says that minoxidil alone **"do[es] not appear to be a sufficient stimulus for hair growth,** particularly in an area affected by alopecia." Id. at col.4, line 63-65.

13) In summary, Bazzano says that without retinoid, *minoxidil just does not work.* Bazzano thus teaches away from my invention.

14) Hoke. Hoke teaches away from my invention. Hoke teaches using nucleotides. Hoke says nucleotides are safe because they are "highly selective" genetic binders and thus do not pose the systemic side effect risk seen with minoxidil or progesterone.

15) In contrast, Hoke admonishes the art to **avoid** progesterone, due to its systemic side effects. Hoke says, "nucleotides targeting 5-alpha reductases have demonstrated the capacity to effectively reduce the synthesis of 5-alpha reductase types 1 or 2. These inhibitors are extremely potent, highly

selective, and should not exhibit any of the side effects produced by the anti-androgens (i.e., feminization or impotency)." Hoke at col. 4, lines 18-24.

16) Hoke similarly says minoxidil does not work: "only 8% of patients reported a dense re-growth of scalp hair." Hoke col.3, line 4-11. Thus, one of skill in the art would interpret Hoke to discourage one from using minoxidil *at all*, alone or with a penetrant.

17) I note also that, contrary to the Examiner's assertion, progesterone and anti-sense nucleotides do not "have the same biological pathway" and do not "work[] via same mechanism." Anti-sense nucleotides ostensibly bind to sense nucleotides coding for 5-alpha reductase polypeptide. They thus ostensibly slow the production of 5-alpha reductase. In contrast, progesterone does not affect 5-alpha reductase translation and production; rather, progesterone competitively binds to the 5-alpha reductase cell-surface receptor. The two types of compounds thus use different biological pathways, working via different mechanisms - one affects intra-cellular genetic transcription and translation, the other affects extra-cellular hormone-receptor communication. This is why,



as Hoke himself says, these two classes of compounds are not known in the art as "interchangeable."

- 18) Secondary Indicia of Non-Obviousness. My invention solves a long felt need. The art cited by the Examiner shows the art has been searching for a patch for minoxidil's well documented shortcomings. I found it. I succeeded where others failed. The art is full of proposed solutions (Hoke, Bradbury, Bazzano, etc. . .). None, however, has achieved my superior results - *ten times* better than minoxidil alone.
- 19) My results were unexpectedly superior. In fact, the art of record confirms that one of skill in the art would have reasonably expected my combinations to not work at all, or to have serious, unwanted systemic side effects. By pursuing thorough testing, over the course of years, and in the face of countervailing bias, I found that my combinations were surprisingly and synergistically effective. My combinations are synergistically effective on more people (85% vs 8%). My compounds produce an effect *qualitatively different* from prior art compounds, growing hair in different locations and growing hair of a different kind.

- 20) The penetration enhancer fundamentally changes the mechanism of the minoxidil or the testosterone blocker. Adding a penetration enhancer to the vascular toner appears to fundamentally change the biological mechanism by which the vascular toner works. This is shown by the qualitatively different results seen between topical minoxidil and my compounds. The two products produce different types of hair, and for different time periods.
- 21) Minoxidil without a penetration enhancer (as available in ROGAINE™ topical minoxidil U.S.P.) produces a different kind of hair than does minoxidil used with a penetration enhancer. It is known in the art that topical minoxidil without a penetration enhancer (as is commercially available in ROGAINE (TM) topical minoxidil U.S.P., commercially available from Pharmacia & Upjohn Inc., Bridgewater, New Jersey) results in thin, baby-like, temporary hair, called "lanugo" hair. My compounds, by contrast, result in good, coarse, "terminal" hair - normal, permanent adult hair.
- 22) This indicates that minoxidil without and with penetration enhancer may act on different types of hair bulbs, or produce different responses from the same hair bulbs. Minoxidil without enhancer is only weakly soluble in polar solvents.

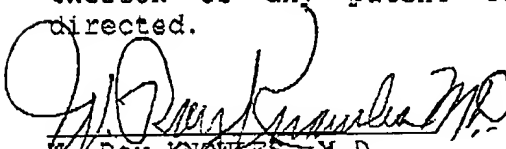
See supra. It thus has difficulty diffusing to the deeply located hair bulbs (roots) which are located just above the deep fat layer. Minoxidil without enhancer may thus affect only hair bulbs located close to the skin surface, or located in a less fatty skin layer, or hair bulbs most sensitive to changes in blood flow. Alternatively, it may affect the same hair bulbs, but with such weak or attenuated effect that the hair bulbs produce a different type of hair.

23) Further, it is known in the art that minoxidil users experience a sudden drop in hair thickness after about thirty months of usage. I thus have tested to identify the time at which my compounds have a sudden drop in effectiveness. Surprisingly, I have found that my compounds apparently do not lose effectiveness at all, even after using them for greater than thirty months. This confirms that while my compounds appear to simply restore or preserve normal hair bulb function, the prior art compositions do not restore normal hair bulb function, but actually provoke an abnormal function - the growth by an adult of baby like hair on adult skin. That this function is abnormal is confirmed by its drop in effectiveness after thirty months; such a drop in efficacy

indicates a "tolerance" acquired against the intervention, rather than the maintenance of a permanent, healthy state.

24) This indicates that the physiological mechanisms and biomedical pathways of my combinations and the prior art compounds are different. Minoxidil alone, in the concentrations typically used, may actually temporarily alter a normal adult body function (causing the adult body to temporarily produce infant hair). In contrast, my invention simply maintains the normal function of the healthy adult body hair bulb, allowing it to continue to produce normal adult hair as long as the compound is used. Penetration enhancer is thus "critical" to the synergy of the claimed compounds.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.

  
W. ROY KNOWLES, M.D.  
February 16, 2001

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Rule 132 Declaration

CURRICULUM VITAE